REMARKS/ARGUMENTS

Claims 23, 24, 26 and 28-37 have been examined. No amendments have been made to the pending claims. Applicants request reconsideration of the claims in view of the remarks below. This communication is being filed in response to the Final Office action dated January 9, 2009 and the Notice of Appeal received by the Office July 15, 2009. Filing of this communication is timely filed Tuesday February 16, 2010, the first business day following the Presidents Day holiday of Monday, February 15, 2010.

Rejections Under 35 U.S.C. § 103:

Claims 23, 31-32, 33-37 remain rejected under 35 USC §103(a) as being obvious over Sallusto *et al.*, (*J. Exp. Med.* 179:1109-1118, 1994), in view of Bigotti *et al.*, (*Prostate* 19:73-87, 1991), as evidenced by Inaba *et al.*, (*J. Exp. Med.* 166:182-194, 1987) for the reasons of record in the paper of October 16, 2007. The Examiner has considered and found Applicants' prior response unconvincing. In particular, the Examiner alleges that Bigotti *et al.* teach that both Langerhans cells and epithelial cells expressing MHC class II molecules are capable of direct antigen presentation to immune cells, and Langerhans cells and HLA class II molecule may provide a mans of eliciting the immune response. Further, the Examiner alleges that Bigotti *et al.* teach that Langerhans cells are antigen presenting cells in this neoplastic environment while HLA class II molecules are expressed by neoplastic epithelium interact primarily or with the aid of Langerhans cells with macrophage and secondarily with T helper lymphocytes causing expansion of cytotoxic T cells and enhancement of the antibody response to membrane-bound tumor associated antigen, therefore providing a means for controlling the escape from the immune surveillance, citing Bigotti *et al.*, page 85, under "Conclusion"). In addition, the Examiner alleges that Bigotti *et al.* teaches that Langerhans cells function as antigen presenting cells, and that these properties are dependent on class II MHC expressions which provides T cell recognition elements for antigen-specific T helper-assisted immune response, such as expansion of cytotoxic T cell clones and enhancement of antibody response (citing page 74, fourth and fifth

paragraphs). The Examiner concludes that the antigen presentation by Langerhans cells to immune cells, and subsequent elicitation of the immune response, as stated in the abstract of Bigotti *et al.*, for example, presentation of the antigen by Langerhans cells to T cells, is clearly prostate cancer antigen because:

1) the immune response, *i.e.*, cytotoxic T cell expansion and the antibody response, are specific to membrane bound prostate tumor antigen in view of the teachings of the abstract and on pages 74 and 85 of Bigotti *et al.*;

2) it is well known that dendritic cells, such as Langerhans cells, stimulate the proliferation response of T cells specific for an antigen after their presentation of the antigen to T cells, as taught by Sallusto *et al.*;

3) it is well known in the art that cancer cell shed their antigen and further, that it is well known in the art that encountering an antigen promotes the maturation and migration of dendritic cells to regional lymph nodes, and presentation of the antigens to naïve T cells by dendritic cells;

Moreover, the Examiner asserts that contrary to the response by Applicants, Bigotti *et al.* teachings of the low abundance of Langerhans cells in prostate cancer actually provides motivation for one to make *in vitro* dendritic cells to administer into prostate cancer patients. The Examiner again alleges that Bigotti *et al.* teaches that low grade carcinomas harbor Langerhans cells, which even if not numerous as, for example, in squamous carcinomas of the epidermis, are nevertheless present, as opposed to the high-grade prostate tumor, and that, similar to other cancers, the presence of Langerhans cells and HLA class II molecules is correlated with good prognosis in prostate cancer. As such, the Examiner has concluded that the low abundance of Langerhans cells in prostate cancer would provide motivation for one to use the method of Sallusto *et al.* to make *in vitro* dendritic cells capable of activating T cells specific for prostate cancer, to administer into prostate cancer patients, to increase the number of dendritic cells in the patient, because i) dendritic cells made by the method of Sallusto *et al.* are

the most potent antigen presentation cells, even more efficient than antigen-specific B cells, as taught by Sallusto *et al.*, and thus complementary to the anti-cancer action of macrophage, and ii) similar to other cancers, the presence of Langerhans cells and HLA class II molecules is correlated with good prognosis in prostate cancer.

The submission by Applicants of Troy *et al.* and Sharma *et al.* has been acknowledged by the Examiner. Applicants' arguments regarding the references has been considered by the Examiner, but not considered persuasive. In particular, the Examiner alleges that Troy *et al.* supports the alleged teachings of Bigotti *et al.* that, although the number of dendritic cells and Langerhans cells in normal tissue were greater than in the normal prostatic tissue, there is, nevertheless, a small amount of activated Langerhans cells in prostate cancer, significantly more than its virtual absence in non-cancerous prostate tissue. The Examiner also notes that it is well known in the art activated Langerhans cells are Langerhans cells that are exposed to, and capture the antigen and has the ability to present the antigen to T cells. As such, the Examiner has concluded that the teaching of Troy *et al.* support the meaning of the teaching of Bigotti *et al.* that Langerhans cells found in a low grade prostate tumor must be present to uptake and present prostate antigen to T cells, and are correlated with good prognosis, especially in view of the teachings in the art that Langerhans cells stimulate a proliferation response of T cells specific for an antigen after their presentation of the antigen to T cells as taught by Sallusto *et al.*, and that encountering an antigen promotes the maturation and migration of dendritic cells to regional lymph nodes, and presentation of the antigen to naïve T cells by Dendritic cells.

As to Sharma *et al.*, the Examiner alleges that there is no indication that the different clones in the Dunning R-3327 rat prostatic adenocarcinoma taught by Sharma *et al.* represent low grade prostate cancer cells in humans. The Examiner also notes that not all Dunning rat prostate cells express IL-10, and as such, which of these clones represent the low grade prostate cancer cells in humans are not described. Moreover, the Examiner has alleged that although in some tumors IL-10 suppresses the immune response, even if low grade prostate

cancer cells secreted IL-10, one cannot predict the effect of IL-10 on the response of the immune response in low-grade prostate cancer, in view of the teachings of Steinbrink *et al.*

Applicants must again strongly disagree with the Examiner rejection of claims 23, 31, 32, and 33-37. In particular, Bigotti *et al.* do not in any way disclose or suggest that the Langerhans cells characterized by binding of anti-S100 polyclonal sera have taken in or begun processing any antigen, much less a prostate specific or prostate tumor associated antigen. It is well known to the artisan of ordinary skill that Langerhans cells are immature antigen presenting cells. In addition, it is well known to the skilled artisan and admitted by the Examiner that immature antigen presenting cells, such as Langerhans cells and immature dendritic cells, once they uptake antigen migrate to a lymph node and that during migration or shortly after arriving at a lymph node become a fully mature antigen presenting cell. It was also well known to an artisan of ordinary skill at the time of the present invention that Langerhans cells also could be induced to migrate to a lymph node when contacted with a inflammatory cytokine and that prostate carcinoma typically secrete inflammatory cytokines.

Bigotti *et al.* as interpreted by the Examiner must be construed to teach the skilled artisan that Langerhans cells in low-grade prostate carcinoma are exposed to, and capture the antigen and have the ability to present the antigen to T cells. In addition, the Examiner asserts that the Langerhans cells are combining with HLA class II expressing prostate epithelial cells to induce prostate specific cytotoxic T cells and macrophage. As above, and in Applicants prior responses Bigotti *et al.* does not teach the artisan of ordinary skill that the Langerhans cells present antigen in low-grade prostate carcinoma. But merely teach that the presence of immature antigen presenting cells, for example, Langerhans cells, is a diagnostic indicator of a good prognosis in low-grade prostate carcinoma. The artisan of ordinary skill at the time of the present invention was well aware of the various issues regarding the immune reaction and surveillance of tumors. It was well known that many tumors, including prostate tumors, produced IL-10 and other cytokines that down regulated the immune response directed against the tumor. See, for example, Sharma *et al.* and other references provided by Applicants.

Further, the Examiner has asserted that the Langerhans cells of Bigotti *et al.* must display a prostate antigen because the immune response, *i.e.*, cytotoxic T cell expansion and the antibody response, are specific to membrane bound prostate tumor antigen in view of the teachings of the abstract and on pages 74 and 85 of Bigotti *et al.* The abstract of Bigotti *et al.* merely states Langerhans cell number is inversely correlated to the histopathological grane and directly to the expression of HLA class II-DR molecules by tumor cells and that the authors believe that this could be important in understanding the more favorable biological behavior of low-grade prostate carcinomas since Langerhans cells and HLA class II molecules may provide a means of eliciting the immune response. These characteristics are known activities of Langerhans cells and HLA class II molecules on whatever cells they appear. There is no suggestion here that the Langerhans cells actually found in the prostate are in the process of taking up prostate antigen or that the cells are in the process of presenting antigen to macrophage in the prostate of low grade prostate carcinoma. As above, and in Applicants prior responses, Langerhans cells are immature antigen presenting cells and must migrate to a lymph node to mature and contact with T cells to produce a cytotoxic T cell response. In addition, also as above and in Applicants prior responses, Bigotti *et al.* did not detect infiltrating lymphocytes which might indicate that antigen presenting cells might have successfully taken up and processed prostate antigen for presentation to naive T cells which would return to the prostate tumor if tumor infiltrating lymphocytes. Further as above, carcinomas, including prostate carcinomas, where known to have an immunosuppressive environment and it was well known that Langerhans cells were present in normal prostate.

The Examiner has noted that Troyer *et al.* did detect activated antigen presenting cells in prostate carcinoma samples. Troyer *et al.* defined these activated cells as dendritic cells, while the Examiner asserted that the activated antigen presenting cells were Langerhans cells. Based on this incorrect assertion the Examiner has concluded that Troyer *et al.* supports the conclusion of Bigotti *et al.* that it is well known in the art that activated Langerhans cells are Langerhans cells that are exposed to, and capture prostate antigen and has the ability to present the antigen to T cells. To the contrary, Troyer *et al.* teaches that there are a few activated

dendritic cells in prostatic carcinoma, not Langerhans cells. There is also no support in Troyer *et al.* that the Langerhans cells detected in prostate low-grade prostate carcinoma by Bigotti *et al.* have been exposed to and have taken up, processed and are presenting prostate specific antigen. As admitted above by the Examiner, the Langerhans cells are immature antigen presenting cells that must mature while migrating to a lymph node where presentation of whatever antigen would take place. As such, Applicants do not agree with the Examiner's combination of the cited references and there would be no *prima facie* reason to combine Bigotti *et al.* with Sallusto *et al.* to stimulate the proliferation response of T cells specific for any prostate antigen.

The Examiner has maintained the rejection of claim 24 under 35 U.S.C. § 103(a) as being obvious over Sallusto *et al.* in view of Bigotti *et al.* and as evidenced by Inaba *et al.* (*supra*), and further in view of Cohen (*Cancer Res.* 54:1055-1058, 1994). The Examiner has consider Applicants prior response and has found it to be unpersuasive. In particular, the Examiner believes that the combination of Sallusto *et al.* and Bigotti *et al.* suggests the compositions of the claims invention as set forth above. Further, the Examiner alleges that it would have been obvious to use as prostate antigen a lysate of prostate cancer cells from a prostate cancer patient for the other reasons of record as recited above.

As above, the combination of Sallusto *et al.* and Bigotti *et al.* fail to teach the compositions of the present invention. Instead, Bigotti *et al.* teach that macrophage likely induce the immune response seen in prostate cancer and that the presence of Langerhans cells can be used to stage prostate cancer tissue. As such, any combination with Inaba *et al.* and/or Cohen *et al.* can not provide the skilled artisan with incentive to combine the references to use a lysate of prostate cancer cells from a prostate cancer patient to make the compositions of the claim 24.

Claim 26 remains rejected under 35 USC §103(a) as being obvious over Sallusto *et al.*, in view of Bigotti *et al.*, and as evidenced by Inaba *et al.*, (*supra*), as applied to claim 23, and further in view of Lutz *et al.* for the reasons already of record. Briefly, the reasons are that the teaching of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* as summarized by the Examiner has

been set forth above and that although the Examiner has concluded that Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.* suggest the compositions of the claimed invention. Therefore, the Examiner believes that it would have been *prima fascia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, using the immortalizing method taught by Lutz *et al.*, because immortalizing dendritic cells would enable maintenance of dendritic cells in vitro for long periods of time, as taught by Lutz *et al.* for the reasons above.

As above, the Sallusto *et al.*, Bigotti *et al.*, and/or Inaba *et al.* when considered either alone or in combination do not teach the compositions of the present invention. As such, the addition of Lutz *et al.* allegedly teaching immortalization of dendritic cells can not provide the skilled artisan with the motivation or guidance to make the composition as set forth in claim 26.

Claims 28-29 remain rejected under 35 USC §103 as being obvious over Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Cohen *et al.*, (*supra*), as applied to claim 23, and further in view of Taylor *et al.* for the reasons of record in Applicants' prior response. Briefly, the Examiner believes that the combination of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* suggests the compositions of the claimed invention. In addition, the Examiner believes that it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Stites (was Inaba *et al.* intended?), and Cohen *et al.*, using the cryopreservation method taught by Taylor *et al.*, to preserve the previously isolated dendritic cells for later use.

Applicants must again disagree with the reasoning of the Examiner. In particular, as above, Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, do not teach the compositions of the present invention. Taylor *et al.* is directed to cryopreservation techniques and does not address the teachings of Bigotti *et al.* Bigotti *et al.* teaches that the immune response is likely induced in prostate cancer by macrophage. As such, Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.*, when

considered individually or in any combination does not teach or suggest the composition as set forth in claims 28 and 29.

Claim 30 remains rejected under 35 USC §103 as being obvious over Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, (*supra*), as applied to claim 23, and further in view of Taylor *et al.* as applied to claim 28, and Lutz *et al.*, for the reasons of record. The Examiner has noted that Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.* suggests the compositions of the claimed invention a set forth above. The Examiner believes that it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.*, using the immortalizing method taught by Lutz *et al.*, because immortalizing dendritic cells would allow maintenance of dendritic cells *in vitro* for long periods of time, as taught by Lutz *et al.*

Applicants must again disagree with the rejection of the Examiner, as above, the teachings of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Taylor *et al.* do not disclose or suggest the compositions of the present application. The teachings of Lutz *et al.* when considered either alone or in combination with any of the other cited references does not cure the deficiencies of the primary references, Sallusto *et al.* and Bigotti *et al.* in that Bigotti *et al.* teaches away from the compositions of the present claims.

In view of the above remarks, Applicants respectfully request the Examiner to reconsider and withdraw the various rejections of claims 23, 24, 26, and 28-37 under 35 U.S.C. § 103(a) as being obvious over Sallusto *et al.*, Bigotti *et al.* as evidenced by Inaba *et al.*, in view of Stites, and Cohen et *al.*, alone and in various combinations. In particular, Bigotti *et al.* teaches away from the compositions of the present invention by teaching that the immune response to prostate cancer is likely induced by macrophage and that Bigotti *et al.* teach no more than a method for staging prostate tumor samples. In light of the teachings of Bigotti *et al.* the skilled artisan would not have been motivated to produce the compositions of the present claims.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 16 February 2010

Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
BWP:kbh
62115002 v1